



ABRIDGED MONOGRAPH

PREPARED BY GATE PHARMACEUTICALS

TEV-TROPIN® is indicated only for the treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone (GH).

Important Safety Information

TEV-TROPIN® stimulates linear growth in children lacking endogenous GH. Treatment of growth hormone-deficient (GHD) children with TEV-TROPIN® produces growth rate and IGF-1 levels similar to those seen after treatment with hGH of pituitary origin.

Unless patients with Prader-Willi Syndrome (PWS) also have a diagnosis of GHD, TEV-TROPIN® is not indicated for treatment of pediatric patients who have growth failure due to genetically confirmed PWS. Because of reported fatalities, patients with PWS who are severely obese, have severe respiratory impairment, respiratory infections, or sleep apnea should interrupt use of GH.

Patients should be observed for evidence of glucose intolerance, hypopituitarism, malignant transformation of skin lesions, hypothyroidism, slipped capital femoral epiphysis, and intracranial hypertension. Fundoscopic examination of patients is recommended at the initiation and periodically during the course of GH treatment. TEV-TROPIN® should not be initiated in patients with acute critical illness as a complication of open heart surgery, abdominal surgery, multiple accidental trauma, or those with acute respiratory failure. TEV-TROPIN® should not be used in patients with evidence of an active malignancy, progressive or recurrent underlying intracranial tumor, active proliferative or severe nonproliferative diabetic retinopathy, or closed epiphysis.

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis.

Somatropin may alter the clearance of drugs metabolized by the CP450 enzyme system and careful monitoring is advisable.

Benzyl alcohol associated with toxicity in newborns is contained in the diluent supplied with TEV-TROPIN®. Treatment of patients with coexisting ACTH deficiency should have glucocorticoid replacement dose adjusted to avoid inhibition of growth.

In studies of growth hormone-deficient children, headaches occurred infrequently. Injection-site reactions (eg, pain, bruise) occurred in 8 of the 164 treated patients.

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1. PRODUCT DESCRIPTION

Brand name, generic

TEV-TROPIN® [somatropin (rDNA origin) for injection]

All dosage forms, including strengths and package sizes

5 mg (15 IU) vial:

Somatropin 5 mg (15 IU)

Mannitol 30 mg

The National Drug Code (NDC) for all formulations

Strength NDC

5 mg vial 57844-713-19

DPS Drug Classification

253.3 Pituitary Dwarfism

253.7 Iatrogenic Pituitary Disorder

253.2 Panhypopituitarism

Clinical Pharmacology/Pharmacokinetics

Clinical trials have demonstrated that TEV-TROPIN® is equivalent in its therapeutic effectiveness and in its pharmacokinetic profile to those of human growth hormone of pituitary origin (somatropin). TEV-TROPIN® stimulates linear growth in children who lack adequate levels of endogenous growth hormone. Treatment of growth hormone-deficient children with TEV-TROPIN® produces increased growth rates and IGF-1 (Insulin-Like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with human growth hormone of pituitary origin.

Both TEV-TROPIN® and somatropin have also been shown to have other actions including:

Clinical Pharmacology

A. Tissue Growth

1. Skeletal Growth. TEV-TROPIN® stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of TEV-TROPIN® results from its effect on the epiphyseal growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient children but increase during treatment with TEV-TROPIN®. Mean serum alkaline phosphatase concentrations are increased.
2. Cell Growth. It has been shown that there are fewer skeletal muscle cells in short statured children who lack endogenous growth hormone as compared with normal children. Treatment with somatropin results in an increase in both the number and size of muscle cells.
3. Organ Growth. Somatropin influences the size of internal organs and it also increases red cell mass.

B. Protein Metabolism

Linear growth is facilitated, in part, by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, results from treatment with somatropin.

C. Carbohydrate Metabolism

Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of somatropin may impair glucose tolerance.

D. Lipid Metabolism

Administration of somatropin to growth hormone-deficient patients mobilizes lipids, reduces body fat stores, and increases plasma fatty acids.

E. Mineral Metabolism

Sodium, potassium, and phosphorous are conserved by somatropin. Serum concentrations of inorganic phosphates increased in patients with growth hormone deficiency after therapy with TEV-TROPIN® or somatropin. Serum calcium concentrations are not significantly altered in patients treated with either somatropin or TEV-TROPIN®.

F. Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Following intravenous administration of 0.1 mg/kg of TEV-TROPIN®, the elimination half-life was about 0.42 hours (approximately 25 minutes) and the mean plasma clearance (\pm SD) was 133 (\pm 16) mL/min in healthy male volunteers.

In the same volunteers, after a subcutaneous injection of 0.1 mg/kg TEV-TROPIN® to the forearm, the mean peak serum concentration (\pm SD) was 80 (\pm 50) ng/mL which occurred approximately 7 hours post-injection and the apparent elimination half-life was approximately 2.7 hours. Compared to intravenous administration, the extent of systemic availability from subcutaneous administration was approximately 70%.

FDA-Approved and Other Studied Indication(s)

TEV-TROPIN® is indicated only for the treatment of children who have growth failure due to inadequate secretion of normal endogenous growth hormone.

Contraindications

TEV-TROPIN® reconstituted with bacteriostatic 0.9% sodium chloride injection, USP (normal saline) (benzyl alcohol preserved) should not be administered to patients with a known sensitivity to benzyl alcohol (see [WARNINGS](#)).

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled clinical trials in non-growth hormone deficient adult patients (n = 522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (see [WARNINGS](#)).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see [WARNINGS](#)). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Warnings/Precautions

Warnings

See [CONTRAINDICATIONS](#) for information on increased mortality in patients with acute critical illnesses due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstructions or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see [CONTRAINDICATIONS](#)).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP. WHEN RECONSTITUTING WITH STERILE NORMAL SALINE, USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

Precautions

General

Therapy with TEV-TROPIN® should be directed by physicians who are experienced in the diagnosis and management of children with growth hormone deficiency.

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas,

in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopy examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

Patients should be monitored carefully for any malignant transformation of skin lesions.

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

As with any protein, local or systemic allergic reactions may occur. Parents/patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients (see PRECAUTIONS, General)

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

Information for Patients

Patients being treated with TEV-TROPIN® (and/or their parents) should be informed about the potential benefits and risks associated with TEV-TROPIN® treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer TEV-TROPIN® should receive appropriate training and instruction

on the proper use of TEV-TROPIN® from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase during somatropin therapy.

Drug Interactions

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11 β HSD-1 enzyme.

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated (see PRECAUTIONS, General).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis and reproduction studies have not been conducted with TEV-TROPIN®.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with TEV-TROPIN®. It is not known whether TEV-TROPIN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TEV-TROPIN® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

There have been no studies conducted with TEV-TROPIN® in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEV-TROPIN® is administered to a nursing woman.

Geriatric Use

The safety and effectiveness of TEV-TROPIN® in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients.

Adverse Reactions

Utilizing a double-antibody immunoassay, no antibodies to growth hormone could be detected in a group of 164 naïve and previously treated clinical trial patients after treatment with TEV-TROPIN® for up to 40 months. However, utilizing the less specific polyethylene glycol (PEG) precipitation immunoassay, 27 of the 164 patient group were tested after treatment with TEV-TROPIN® for 4 to 6 months and antibodies to growth hormone were detected in two patients (7.4%). The binding capacity of the antibodies from the two antibody positive patients was not determined.

None of the patients with anti-GH antibodies in the clinical studies experienced decreased linear growth response to TEV-TROPIN® or any other associated adverse event. Growth hormone antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases, when binding capacity exceeds 2 mg/L, growth attenuation has been observed.

In studies of growth hormone-deficient children, headaches occurred infrequently. Injection site reactions (e.g., pain, bruise) occurred in 8 of the 164 treated patients.

Leukemia has been reported in a small number of patients treated with other growth hormone products. It is uncertain whether this risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors.

Dosage, Administration and Availability

Dosage and Administration

A dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight administered 3 times per week by subcutaneous injection is recommended. The dosage schedule for TEV-TROPIN® should be individualized for each patient. Subcutaneous injection of greater than 1 mL of reconstituted solution is not recommended.

After the dose has been determined, each vial of TEV-TROPIN® should be reconstituted with 1 to 5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved).^{*} The stream of normal saline should be aimed against the side of the vial to prevent foaming. Swirl the vial with a GENTLE rotary motion until the contents are completely dissolved and the solution is clear. DO NOT SHAKE. Since TEV-TROPIN® is a protein, shaking or vigorous mixing will cause the solution to be cloudy. If the resulting solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

^{*} Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP.

Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for proteins like TEV-TROPIN® growth hormone. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted, the contents MUST NOT be used.

Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. It is recommended that TEV-TROPIN® be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

Overdosage

The recommended dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight 3 times per week should not be exceeded. Acute overdose could cause initial hypoglycemia and subsequent hyperglycemia. Repeated use of doses in excess of those recommended could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

Stability and Storage

Before Reconstitution – Vials of TEV-TROPIN® are stable when refrigerated at 36° to 46°F (2° to 8°C). Expiration dates are stated on the labels.

After Reconstitution – Vials of TEV-TROPIN® are stable for up to 14 days when reconstituted with bacteriostatic 0.9% sodium chloride (normal saline), USP, and stored in a refrigerator at 36° to 46°F (2° to 8°C). Do not freeze the reconstituted solution.

How Supplied

TEV-TROPIN® (somatropin, rDNA origin, for injection) is supplied as 5 mg (15 IU) of lyophilized, sterile somatropin per vial, in a box containing one vial of TEV-TROPIN® (5 mg per vial) and one vial of diluent [5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved)].

Co-Prescribed/Concomitant Therapies

Patient treatment must be individualized. (See WARNINGS/PRECAUTIONS.)

2. PLACE OF PRODUCT IN THERAPY

The prevalence of growth hormone deficiency in children in the United States has been estimated between 10,000 to 15,000. Since 1985, recombinant human growth hormone has been available on the market. Its efficacy and safety in children with growth failure due to inadequate secretion of normal endogenous growth hormone have been demonstrated in several clinical trials, including the present study with TEV-TROPIN®.

Treatment with recombinant growth hormone has been shown to have positive effects on linear growth. Growth hormone replacement improves height and weight velocity, increases insulin-like growth factor 1 (IGF-1), and exhibits no unexpected changes in Tanner maturation scores. Furthermore, the adverse events observed with TEV-TROPIN®, which included localized erythema, itching at the injection site, slipped capital femoral epiphysis, and craniopharyngioma, were similar to other recombinant growth hormone products available on the market. With its efficacy and safety profile, TEV-TROPIN® represents another viable alternative for recombinant human growth hormone in the treatment of children diagnosed with growth hormone deficiency.

3. SUPPORTING CLINICAL INFORMATION

Safety and Efficacy of Recombinant Human Growth Hormone (rhGH) in Children With Short Stature Due to Growth Hormone Deficiency (GHD): A Cumulative Progress Report on Phase II and III Clinical Trial Data

Materials and Methods

Study Drug

Somatropin (human growth hormone, rDNA origin) manufactured by Bio-Technology General (BTG) Corporation, was supplied as single-use 7 mg vials.

Study Objective

The objective of this study was to determine the efficacy and safety of human growth hormone (hGH) in children with short stature due to growth hormone deficiencies.

Patient Selection

The patient population consisted of 163 children referred for poor linear growth and diagnosed as GH deficient. Patients were selected for study if they were euthyroid, between 2 and 18 years old, and had exhibited growth rates less than 5 cm/yr in patients less than 5 years old and less than 4.5 cm/yr in patients 5 to 18 years old, based on a minimum of four months of data. GHD was demonstrated by inadequate GH secretion (defined as peak GH response of less than 10 ng/mL) during two standard stimulation tests, or total GH levels less than 3.5 ng/mL during a 24-hour integrated concentration GH test (IC-GH). Patients must have exhibited bone age delay equal to or exceeding 2 standard deviations for age when analyzed by the method of Greulich and Pyle (1959). Patients who developed GHD secondary to treatment for craniopharyngioma must have been stable and off radiation therapy for a minimum of 6 months prior to entering the study. Signed informed consent documents were obtained from the patients or their legal representatives.

Patients were excluded if they had been diagnosed with Turner's syndrome, had been treated with any preparation of GH within 6 months prior to the start of the study, or had severe congenital heart disease, chronic infection, chronic renal disease, malabsorption syndrome, regional ileitis, diabetes, or psychosocial dwarfism. Patients whose thyroid-stimulating hormone (TSH) deficiency could not be maintained in the euthyroid state by oral medication during the prestudy period were excluded, as were patients on glucocorticoid replacement therapy greater than 15 mg/m²/day of hydrocortisone. Patients whose laboratory tests were clinically significantly abnormal were excluded. Patients with histories of malignancies or other major systemic diseases, which, in the opinion of the investigator and/or the clinical coordinator, rendered the patient unsuitable for inclusion in the study, were excluded.

Protocol

The study was conducted over three phases: Prestudy Evaluation Period, Phase II (Day 1 to Week 24), and Phase III (Beyond Week 24 Through 2 Years of Therapy). Dosing regimen was 0.3 mg/kg/week, divided into three doses.

Prestudy Evaluation Period — During this period, potential patients submitted their signed informed consent forms and were tested for GHD. Each child underwent pharmacological stimuli with clonidine, L-dopa, insulin, or arginine. If necessary, children also underwent the IC-GH test. Standard laboratory tests were performed for blood chemistry, IGF-1 (somatomedin-C), CBC with differential, platelets, glycosolated hemoglobin [Hgb A_{1c}], urinalysis, thyroxine (T₄), thyroid-stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone or estradiol. A medical history was taken, and a physical examination was performed, including height measurement by stadiometer, weight, Tanner staging, and bone age determination. Baseline blood was drawn for comparison in later testing for antibodies to GH and *Escherichia coli* protein. Patients meeting entrance criteria entered Phase II of the study.

Phase II — On Day 1 of Phase II, each patient underwent a baseline physical examination, including laboratory testing, if Prestudy data were more than 6 months old. Following physical examination and laboratory tests, continuous somatropin was begun at a dose of 0.3 mg/kg/week, given as three doses a week. During Phase II, patients were reevaluated at Weeks 1, 4, 8, 16, and 24. Each reevaluation included a physical examination, antibody tests, and laboratory tests. At Week 24, bone age and Hgb A_{1c} were determined. At each visit, each patient was evaluated for compliance with the protocol, and the development of adverse experiences. Patients successfully completing Phase II advanced to Phase III.

Phase III — During Phase III, patients were reevaluated at Months 8, 10, 12, 15, 18, 21, and 24. At each visit, each patient was evaluated for compliance with the protocol and the development of adverse experiences. Each visit included a physical examination, antibody tests, and laboratory tests. At Months 12 and 24, bone age and Hgb A_{1c} levels were again determined.

Data Analysis

Patient Classification

The patients were classified into five strata, according to the prestudy hGH test response/level:

a) Naïve (previously untreated):

- 1) Type I: At least two provocative pharmacologic tests, and hGH response <10 ng/mL on each of them.
- 2) Type II: hGH response ≥ 10 ng/mL on at least one provocative test; integrated concentrations of hGH level <3.5 ng/mL.
- 3) Type II*: No provocative test; integrated hGH level <3.5 ng/mL.

b) Non-Naïve (previously treated):

- 1) Recent: Treatment continued up to Day 1.
- 2) Non-recent: Treatment stopped at least six months prior to Day 1.*

*This group allows presentation of two patients entered into study despite exclusion criteria requiring non-naïve patients to be off GH therapy for six months.

Height (or Weight) Velocity

Velocity was calculated at Day 1 by referencing the latest measurement that was taken at least 105 days previously, and then from Day 1 cumulatively to each subsequent visit. Velocity gives a meaningful context for evaluating the efficacy of hGH therapy, but the validity of a Day 1 velocity for non-naïve patients is questionable. To compare the efficacy in non-naïve patients, we also evaluated the change in Z-scores or status for height and weight.

Height (or Weight) Z-Score (or Status)

Z-score is the deviation from the population mean in standard deviation units. Negative values denote heights (or weights) below the population mean. "Population" is determined by the patient's gender and age. Calculations in this study used percentiles of the height and weight of U.S. children. For a child of a given gender and age, the Hamill data were interpolated to obtain: U = 95th percentile; M = 50th percentile; L = 5th percentile. The formula for standard deviation (SD) is: $SD = (U - L)/3.28$. The formula for Z-score is: $Z\text{-score} = (x - M)/SD$, where x = height (or weight).

Changes in Blood Chemistry and Hematology

Changes in clinical laboratory test values are indicated by categorical "grades," with ± 1 denoting a relatively mild change (increase [+1], decrease [-1]) and ± 2 denoting a more serious change from pretreatment values (increase [+2], decrease [-2]). While these grades are arbitrary, they were helpful in manipulating the large body of data generated by clinical laboratory tests.

Efficacy Results

The study collected data on 163 patients treated in 11 centers: 7 in the United States and 4 in Israel. Of the 163 patients, 67 were Naïve Type I, 60 were Naïve Type II (1 of those did not have provocation testing), 34 were Non-Recent Non-Naïve, and 2 were Recent Non-Naïve. Patients ranged in age from 2.6 years to 17.8 years, with a mean age of 11 years. One hundred nineteen of the patients (73%) were male, and 44 of the patients (27%) were female. One hundred twenty seven of the patients (78%) were naïve, or not previously treated with hGH, and 36 patients (22%) were non-naïve. In 72 of the 163 patients, the etiology of GHD was idiopathic. Compliance was evaluated at each follow-up visit. Only two patients missed more than 7 single injections during the course of this study.

Five patients (3%) withdrew from the study at various times and for various reasons. An 11-year-old female, Naïve II, with a history of GHD, was not eating properly due to difficulties at home. She was withdrawn by the investigator after 12 months. An 11-year-old male, Naïve II*, with a history of growth hormone deficiency and hyperactivity, was withdrawn. The physician, when evaluating response to therapy, discovered that the pretreatment height data had been recorded incorrectly. The patient did not meet the entrance criteria, and the investigator withdrew the patient from the study after 9 months. A 15-year-old male, Non-Naïve, with a history of panhypopituitarism, mental retardation, cerebral palsy, muscle contractions, and seizures, was withdrawn. Due to difficulty assessing height, noncompliance, and the need for initiation of androgen therapy, the patient was withdrawn after 24 weeks of therapy. A 6-year-old male, Naïve I, with a history of panhypopituitarism, septo-optic dysplasia, and seizures, was withdrawn after one injection in one week of therapy for

noncompliance. A 14-year-old male, Non-Naïve, with a history of panhypopituitarism, was withdrawn by his parents, who elected to treat their son with pituitary-derived hGH, which was available in Israel.

In 89 patients, the Day 1 growth rate value was higher than the Prestudy value. For 69 patients, the Day 1 value was lower. For 3 patients, the Prestudy period was less than 105 days, preventing the calculation of a Day 1 growth rate. Two patients had no Day 1 height data available, since patients just entered the study. Of 36 non-naïve patients in the study, the number of days since previous hGH treatment ranged from 0 to 1547, with a median of 363 days.

Height Velocity and Height Z-Score (or Status)

Patients in each of the groups Naïve I, Naïve II, and Non-Naïve exhibited statistically significant ($P < 0.01$) mean cumulative increases in height velocity and height Z-score or Status at Week 24 and at the latest in-treatment measurement.

Pretreatment Height

		Naïve Type I	Naïve ¹ Type II	Non-Naïve ²	Recent Non-Naïve ³
Prestudy Velocity (cm/yr)	average ⁴	2.87	3.36	2.22	9.29
	avg. SD	1.13	0.88	1.10	—
	n	66	58	34	2
Day 1 Height (cm)	average ⁴	118.4	125.3	121.6	148.3
	avg. SD	15.7	11.7	11.7	—
	n	65	58	34	2
Day 1 Z-Score ⁵ (avg)	average ⁴	-3.38	-2.88	-4.03	-2.73
	SD	0.92	0.67	0.94	—
	n	65	58	34	2
Day 1 Velocity (cm/yr) (avg SD)	average ⁴	3.16	3.77	2.83	5.71
	SD	1.85	1.36	1.51	—
	n	64	58	34	2

¹ Includes one Type II*

² Off hGH >6 months

³ On hGH up to start of study

⁴ Both “average” and “avg. SD” are the weighted mean value obtained from individual study centers

⁵ Deviation from Hamill data median.

Change in Height
(Cumulative to Week 24)

		Naïve Type I	Naïve ¹ Type II	Non-Naïve ²	Recent Non-Naïve ³
Week 24 Value					
Change in Velocity (cm/yr)	average ⁴	6.36	4.37	6.28	0.28
	<i>P</i>	<.01	<.01	<.01	—
	<i>n</i>	49	40	34	1
Change in Z-Score (e) (SD)	average ⁴	0.35	0.21	0.32	0.26
	<i>P</i>	<.01	<.01	<.01	—
	<i>n</i>	50	40	33	1

Change in Height
(Cumulative to Latest Value)

		Naïve Type I	Naïve ¹ Type II	Non-Naïve ²	Recent Non-Naïve ³
Latest Value in Study					
Change in Velocity (cm/yr)	average ⁴	5.57	4.42	5.26	-1.30
	<i>P</i>	<.01	<.01	<.01	—
	<i>n</i>	63	48	34	1
Change in Z-Score ⁵ (SD)	average ⁴	0.46	0.24	0.48	0.31
	<i>P</i>	<.01	<.01	<.01	—
	<i>n</i>	63	58	33	1

¹ Includes one Type II*

² Off hGH >6 months

³ On hGH up to start of study

⁴ Weighted mean value obtained from individual study centers

⁵ Deviation from Hamill data median.

On Day 1, the heights of all patients in the study were below the 10th percentile, and only two were above the 5th percentile. In most cases, patients before therapy had Day 1 height velocities less than the medians for their ages and genders. After treatment, their height velocities exceeded the medians, indicating that their velocities not only increased, but that the acceleration was greater than “normal” (i.e., “catch-up”) growth.

On Day 1, the height Z-scores of all patients in the study were well below the norm for their genders and ages. At the latest in-treatment measurement, all patients exhibited changes in height Z-score that brought them closer to the median for their genders and ages.

Weight Velocity and Weight Z-Score

Patients in each of the groups Naïve I, Naïve II, and Non-Naïve exhibited statistically significant ($P<0.05$) mean cumulative increases in weight velocity and status or Z-Score at Week 24 and at the latest in-treatment measurement.

Tanner Maturation Scores

Tanner maturation scores increased for less than 13% of patients, a percentage consistent with the age distribution of the study population. Conformation variables used were arm span/height and lower body segment/height ratio. Results were expressed as percentages to observe changes in body proportionality.

Safety Results

Clinical laboratory data were obtained at specified intervals for blood chemistry, hematology, and urinalysis.

Blood Chemistry

Overall, mean fasting blood chemistry values showed no clinically significant changes between Day 1 and Week 24, with the exceptions of inorganic phosphorous and alkaline phosphatase. Changes in these values are known to parallel the physiologic effects of GH on skeletal growth.

Hematology

Tests of hematology parameters showed no clinically significant changes throughout the study. Most abnormal values resolved by the next visit or still under observation. Transient elevations in erythrocyte sedimentation rate occurred in 28 patients. No clinically significant changes in Hgb A_{1c} occurred throughout the study.

Urinalysis

No clinically significant elevations in urinary protein, urinary glucose, or urinary hemoglobin occurred throughout the study.

Thyroid

All study patients were required to demonstrate euthyroidism before starting treatment. After initiation of hGH therapy, patients were monitored for signs of clinical hypothyroidism. Levels of T4 and TSH were also monitored. No clinically significant changes in TSH were noted, and no patient was judged to be clinically hypothyroid once treatment started.

IGF-1

The mean level of IGF-1 (somatomedin-C) rose significantly throughout the study, from a mean pretreatment or Day 1 level (U/mL) of 0.7 ± 0.1 ($P < 0.01$) to a Month 12 level of 1.6 ± 0.3 .

Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Estradiol, and Testosterone

There were no clinically significant changes in mean LH or FSH levels during the study. Testosterone levels exceeded the prepubertal limit (50 ng/dL) in 28 males (23%) over the course of the study. Estradiol levels exceeded the prepubertal limit (15 pg/mL) in 10 females (23%) during the study. Most of the elevations occurred late in the study period.

hGH Antibody

Patients were evaluated throughout the study for antibodies to hGH. Samples were tested using a double antibody radio-immune assay (RIA). There was no trend toward antibody development throughout the study.

Adverse Experiences

Adverse experiences (AEs) were monitored in 126 patients who had completed week 24 of the study. The majority of AEs were typical childhood illnesses: upper respiratory tract infection, otitis media, febrile episode, headache, and cough. AEs were also monitored throughout the entire study period. Of the AEs from the entire study period that presented special concerns (e.g., enlarged liver, swelling and pain in the knee, seizure), only one (non-pitting edema) was considered related to the study drug.

During the study, two patients were diagnosed with craniopharyngioma. One patient was diagnosed by computed tomography (CT) scan 8 weeks after starting therapy. The other patient experienced a recurrence of craniopharyngioma that had been first diagnosed 11 years prior to enrollment, and subsequently removed in several craniotomies. Both patients were under close observation.

AE data collected in the study were compared to previously published AE data collected in 239 patients treated with an FDA-approved hGH (Humatrope® [somatropin (rDNA origin) for injection], Eli Lilly & Company). The overall incidence of AEs with an incidence of greater than 1% did not differ between the two study drugs.

Discussion

Efficacy

In congruence with several clinical studies, monographs, and symposia around the world, the study of 163 patients with short stature due to GH deficiency, treated for up to 17 months, confirmed the safety and efficacy of hGH. Efficacy points included enhanced longitudinal growth, increases in IGF-1, and no unexpected changes in Tanner maturation scores.

Height Velocity and Z-Score

By the end of 24 weeks of therapy, significant ($P<0.01$) mean increases in height velocity were experienced by patients in the Naïve I (6.4 cm/yr over baseline), Naïve II (4.4 cm/yr over baseline), and Non-Naïve (6.3 cm/yr over baseline) strata. Similarly, patients experienced statistically significant ($P<0.01$) mean increases in height Z-score over baseline in all three strata: Naïve I (0.35 standard deviations over baseline), Naïve II (0.21 standard deviations over baseline), and Non-Naïve (0.32 standard deviations over baseline).

Weight Velocity and Z-Score

Statistically significant ($P<0.05$) mean increases in weight velocity were experienced by patients in the Naïve I (1.8 kg/yr over baseline), Naïve II (3.1 kg/yr over baseline), and Non-Naïve (1.5 kg/yr over baseline) strata by 24 weeks of treatment. Likewise, patients experienced significant ($P<0.01$) increases in weight Z-score over baseline in all three strata: Naïve I (0.11 standard deviations over baseline), Naïve II (0.13 standard deviations over baseline), and Non-Naïve (0.10 standard deviations over baseline).

Tanner Maturation Scores

Long-term hGH replacement therapy in other clinical studies has not been shown to cause unexpected shifts in the normal maturation process. Similarly, the Tanner maturation scores for the patients in this study did not show any hastening of the maturation process.

IGF-1

Studies of patients undergoing hGH replacement therapy have established the elevation of serum IGF-1 (somatomedin-C) levels during therapy. The findings in the patients in this study mirrored those findings, with levels of serum IGF-1 increasing significantly over the first month of therapy, then rising for 6 months to a plateau level where they remained for the balance of therapy.

Safety

Serum Chemistry

Monitoring of routine serum chemistries in the patient population for this study confirmed the findings of other clinical studies. Serum alkaline phosphatase and serum phosphorous were increased by hGH therapy. These are expected changes, mirroring the physiologic effects of active skeletal growth. As other investigators have found, there was a slight decrease in serum blood urea nitrogen.

Blood Glucose

There was no clinically significant rise in mean glucose levels among the patients in this study. This is consistent with other studies that have found that overt glucose intolerance is extremely uncommon with currently used hGH dosing schedules.

Hematology

The results of this study found no significant changes in hematology. Several other studies of hGH therapy have looked at hemoglobin, red blood count and platelet count and found no significant differences from baseline values.

Urinalysis

There were no significant changes in urinalysis values in the patient population, confirming the findings of other investigators.

Thyroid Function

There is a substantial body of conflicting evidence on the effect of GH therapy on thyroid function in GH-deficient children with idiopathic hypopituitarism. Several researchers have concluded that hGH therapy induces hypothyroidism. Other investigators have come to the conclusion that the risk of inducing hypothyroidism is slight. On balance, it appears that some researchers believe that, for a small percentage of patients with hypopituitarism, there is a slight propensity toward hypothyroidism during hGH therapy.

No patient in this study was judged to be clinically hypothyroid, and no patients required supplemental thyroid hormone.

IGF-1

Levels of IGF-1 rose significantly within one month and reached a plateau at an elevated level at 6 months. These findings are throughout the study, consistent with the findings of other studies of this parameter.

Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Estradiol, and Testosterone

While hGH therapy enhanced the growth of patients, there is no evidence in the literature that hGH affected the rate at which patients achieved sexual maturation. In 23% of males in the study, testosterone levels increased beyond prepubertal limits. In 23% of females in the study, estradiol levels increased above prepubertal limits. There were no significant changes in LH and FSH during this study.

hGH Antibodies

Patients receiving early preparations of pituitary-derived hGH (p-hGH) developed anti-hGH antibodies, and most experienced attenuated growth following treatment. Transition to recombinant hGH resulted in a significant rise in antibody levels, caused by high levels of *E. coli* protein. As methods of production of hGH were refined, however, development of antibodies dropped. In 1987, Eli Lilly reported that, of 481 patients receiving Humatrope®, 1.7% developed antibodies, compared to 74.5% of patients receiving early preparations of somatrem (hGH).

The double-antibody assay method of antibody detection was similar to that used by Lilly and by Genentech. The somatropin (hGH) used in this study produced no antibodies in any sample from any treated patient, regardless of duration of treatment. While these results do not rule out antibody production, it does indicate that potential antibody will be at a low level, with negligible binding capacity.

Adverse Experiences

Before 1985, the only significant AEs in children treated with hGH have been the development of antibodies (to early preparations) and the transmission of Creutzfeldt-Jakob disease. Both of these AEs are related to the preparation of the hGH, and not to the biological action of the hormone. In the experience of several investigators over the course of many years, hGH therapy leads to very few AEs. Other AEs reported included localized erythema, itching at the injection site, slipped capital femoral epiphysis, and craniopharyngioma.

Of the 163 patients treated in this study, one patient experienced a slipped femoral epiphysis. Researchers have calculated the occurrence of slipped upper femoral epiphysis at 2 to 13 per 100,000 children. The overall AE profile of somatropin is comparable to that of Humatrope®. It should be noted that neither study involved a placebo treatment group; hence, it is impossible to isolate AEs associated with intercurrent illnesses and events.

Conclusion

The somatropin administered in this study promoted an increase in height and weight velocity in pediatric patients suffering from GHD. The product was approved in the United States in 2002 under the brand name TEV-TROPIN®.

4. BIBLIOGRAPHY AND APPENDICES

A copy of the official product labeling

Data on file. Gate Pharmaceuticals.

5. FULL PRESCRIBING INFORMATION

Description

TEV-TROPIN® (somatropin, rDNA origin, for injection), a polypeptide of recombinant DNA origin, has 191 amino acid residues and a molecular weight of about 22,124 daltons. It has an amino acid sequence identical to that of human growth hormone of pituitary origin. TEV-TROPIN® is synthesized in a strain of *Escherichia coli* modified by insertion of the human growth hormone gene.

TEV-TROPIN® is a sterile, white, lyophilized powder, intended for subcutaneous administration, after reconstitution with bacteriostatic 0.9% sodium chloride injection, USP, (normal saline) (benzyl alcohol preserved). The quantitative composition of the lyophilized drug per vial is:

5 mg (15 IU) vial:
Somatropin 5 mg (15 IU)
Mannitol 30 mg

The diluent contains bacteriostatic 0.9% sodium chloride injection, USP, (normal saline), 0.9% benzyl alcohol as a preservative, and water for injection. A 5 mL vial of the diluent will be supplied with each dispensed vial of TEV-TROPIN®.

TEV-TROPIN® is a highly-purified preparation. Reconstituted solutions have a pH in the range of 7.0 to 9.0.

Clinical Pharmacology

Clinical trials have demonstrated that TEV-TROPIN® is equivalent in its therapeutic effectiveness and in its pharmacokinetic profile to those of human growth hormone of pituitary origin (somatropin). TEV-TROPIN® stimulates linear growth in children who lack adequate levels of endogenous growth hormone. Treatment of growth hormone-deficient children with TEV-TROPIN® produces increased growth rates and IGF-1 (Insulin-Like Growth Factor/Somatomedin-C) concentrations that are similar to those seen after therapy with human growth hormone of pituitary origin.

Both TEV-TROPIN® and somatropin have also been shown to have other actions including:

A. Tissue Growth

1. **Skeletal Growth.** TEV-TROPIN® stimulates skeletal growth in patients with growth hormone deficiency. The measurable increase in body length after administration of TEV-TROPIN® results from its effect on the epiphyseal growth plates of long bones. Concentrations of IGF-1, which may play a role in skeletal growth, are low in the serum of growth hormone-deficient children but increase during treatment with TEV-TROPIN®. Mean serum alkaline phosphatase concentrations are increased.
2. **Cell Growth.** It has been shown that there are fewer skeletal muscle cells in short statured children who lack endogenous growth hormone as compared with normal children. Treatment with somatropin results in an increase in both the number and size of muscle cells.
3. **Organ Growth.** Somatropin influences the size of internal organs and it also increases red cell mass.

B. Protein Metabolism

Linear growth is facilitated, in part, by increased cellular protein synthesis. Nitrogen retention, as demonstrated by decreased urinary nitrogen excretion and serum urea nitrogen, results from treatment with somatropin.

C. Carbohydrate Metabolism

Children with hypopituitarism sometimes experience fasting hypoglycemia that is improved by treatment with somatropin. Large doses of somatropin may impair glucose tolerance.

D. Lipid Metabolism

Administration of somatropin to growth hormone-deficient patients mobilizes lipid, reduces body fat stores, and increases plasma fatty acids.

E. Mineral Metabolism

Sodium, potassium, and phosphorous are conserved by somatropin. Serum concentrations of inorganic phosphates increased in patients with growth hormone deficiency after therapy with TEV-TROPIN® or somatropin. Serum calcium concentrations are not significantly altered in patients treated with either somatropin or TEV-TROPIN®.

F. Connective Tissue Metabolism

Somatropin stimulates the synthesis of chondroitin sulfate and collagen as well as the urinary excretion of hydroxyproline.

Pharmacokinetics

Following intravenous administration of 0.1 mg/kg of TEV-TROPIN®, the elimination half-life was about 0.42 hours (approximately 25 minutes) and the mean plasma clearance (\pm SD) was 133 (\pm 16) mL/min in healthy male volunteers.

In the same volunteers, after a subcutaneous injection of 0.1 mg/kg TEV-TROPIN® to the forearm, the mean peak serum concentration (\pm SD) was 80 (\pm 50) ng/mL which occurred approximately 7 hours post-injection and the apparent elimination half-life was approximately 2.7 hours. Compared to intravenous administration, the extent of systemic availability from subcutaneous administration was approximately 70%.

Indication and Usage

TEV-TROPIN® is indicated only for the treatment of children who have growth failure due to an inadequate secretion of normal endogenous growth hormone.

Contraindications

TEV-TROPIN® reconstituted with bacteriostatic 0.9% sodium chloride injection, USP (normal saline) (benzyl alcohol preserved) should not be administered to patients with a known sensitivity to benzyl alcohol (see [WARNINGS](#)).

Somatropin should not be used for growth promotion in pediatric patients with closed epiphyses.

Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

In general, somatropin is contraindicated in the presence of active malignancy. Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Somatropin should be discontinued if there is evidence of recurrent activity. Since growth hormone deficiency may be an early sign of the presence of a pituitary tumor (or, rarely, other brain tumors), the presence of such tumors should be ruled out prior to initiation of treatment. Somatropin should not be used in patients with any evidence of progression or recurrence of an underlying intracranial tumor.

Somatropin should not be used to treat patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. Two placebo-controlled

clinical trials in non-growth hormone deficient adult patients (n = 522) with these conditions in intensive care units revealed a significant increase in mortality (41.9% vs. 19.3%) among somatropin-treated patients (doses 5.3 to 8 mg/day) compared to those receiving placebo (see [WARNINGS](#)).

Somatropin is contraindicated in patients with Prader-Willi syndrome who are severely obese or have severe respiratory impairment (see [WARNINGS](#)). Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Warnings

See [CONTRAINDICATIONS](#) for information on increased mortality in patients with acute critical illnesses due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure. The safety of continuing somatropin treatment in patients receiving replacement doses for approved indications who concurrently develop these illnesses has not been established. Therefore, the potential benefit of treatment continuation with somatropin in patients having acute critical illnesses should be weighed against the potential risk.

There have been reports of fatalities after initiating therapy with somatropin in pediatric patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstructions or sleep apnea, or unidentified respiratory infection. Male patients with one or more of these factors may be at greater risk than females. Patients with Prader-Willi syndrome should be evaluated for signs of upper airway obstruction and sleep apnea before initiation of treatment with somatropin. If during treatment with somatropin, patients show signs of upper airway obstruction (including onset of or increased snoring) and/or new onset sleep apnea, treatment should be interrupted. All patients with Prader-Willi syndrome treated with somatropin should also have effective weight control and be monitored for signs of respiratory infection, which should be diagnosed as early as possible and treated aggressively (see [CONTRAINDICATIONS](#)).

Unless patients with Prader-Willi syndrome also have a diagnosis of growth hormone deficiency, TEV-TROPIN® is not indicated for the treatment of pediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome.

Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP. WHEN RECONSTITUTING WITH STERILE NORMAL SALINE, USE ONLY ONE DOSE PER VIAL AND DISCARD THE UNUSED PORTION.

Precautions

General

Therapy with TEV-TROPIN® should be directed by physicians who are experienced in the diagnosis and management of children with growth hormone deficiency.

Treatment with somatropin may decrease insulin sensitivity, particularly at higher doses in susceptible patients. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during somatropin treatment. Therefore, glucose levels should be monitored periodically in all patients treated with somatropin, especially in those with risk factors for diabetes mellitus, such as obesity (including obese patients with Prader-Willi syndrome), Turner syndrome, or a family history of diabetes mellitus. Patients with preexisting type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during somatropin therapy. The doses of antihyperglycemic drugs (i.e., insulin or oral agents) may require adjustment when somatropin therapy is instituted in these patients.

Patients with preexisting tumors or growth hormone deficiency secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process. In pediatric patients, clinical literature has

revealed no relationship between somatropin replacement therapy and central nervous system (CNS) tumor recurrence or new extracranial tumors. However, in childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumors, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms. In adults, it is unknown whether there is any relationship between somatropin replacement therapy and CNS tumor recurrence.

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with somatropin products. Symptoms usually occurred within the first eight (8) weeks after the initiation of somatropin therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the somatropin dose. Funduscopic examination should be performed routinely before initiating treatment with somatropin to exclude preexisting papilledema, and periodically during the course of somatropin therapy. If papilledema is observed by funduscopy during somatropin treatment, treatment should be stopped. If somatropin-induced IH is diagnosed, treatment with somatropin can be restarted at a lower dose after IH-associated signs and symptoms have resolved. Patients with Turner syndrome, chronic renal insufficiency, and Prader-Willi syndrome may be at increased risk for the development of IH.

In patients with hypopituitarism (multiple hormone deficiencies), standard hormonal replacement therapy should be monitored closely when somatropin therapy is administered.

Undiagnosed/untreated hypothyroidism may prevent an optimal response to somatropin, in particular, the growth response in children. Patients with Turner syndrome have an inherently increased risk of developing autoimmune thyroid disease and primary hypothyroidism. In patients with growth hormone deficiency, central (secondary) hypothyroidism may first become evident or worsen during somatropin treatment. Therefore, patients treated with somatropin should have periodic thyroid function tests and thyroid hormone replacement therapy should be initiated or appropriately adjusted when indicated.

Patients should be monitored carefully for any malignant transformation of skin lesions.

When somatropin is administered subcutaneously at the same site over a long period of time, tissue atrophy may result. This can be avoided by rotating the injection site.

As with any protein, local or systemic allergic reactions may occur. Parents/patients should be informed that such reactions are possible and that prompt medical attention should be sought if allergic reactions occur.

Pediatric Patients (see Precautions, General)

Slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders (including pediatric growth hormone deficiency and Turner syndrome) or in patients undergoing rapid growth. Any pediatric patient with the onset of a limp or complaints of hip or knee pain during somatropin therapy should be carefully evaluated.

Progression of scoliosis can occur in patients who experience rapid growth. Because somatropin increases growth rate, patients with a history of scoliosis who are treated with somatropin should be monitored for progression of scoliosis. However, somatropin has not been shown to increase the occurrence of scoliosis. Skeletal abnormalities including scoliosis are commonly seen in untreated Turner syndrome patients. Scoliosis is also commonly seen in untreated patients with Prader-Willi syndrome. Physicians should be alert to these abnormalities, which may manifest during somatropin therapy.

Information for Patients

Patients being treated with TEV-TROPIN® (and/or their parents) should be informed about the potential benefits and risks associated with TEV-TROPIN® treatment. This information is intended to better educate patients (and caregivers); it is not a disclosure of all possible adverse or intended effects.

Patients and caregivers who will administer TEV-TROPIN® should receive appropriate training and instruction on the proper use of TEV-TROPIN® from the physician or other suitably qualified health care professional. A puncture-resistant container for the disposal of used syringes and needles should be strongly recommended. Patients and/or parents should be thoroughly instructed in the importance of proper disposal, and cautioned against any reuse of needles and syringes. This information is intended to aid in the safe and effective administration of the medication.

Laboratory Tests

Serum levels of inorganic phosphorus, alkaline phosphatase, parathyroid hormone (PTH) and IGF-1 may increase during somatropin therapy.

Drug Interactions

Somatropin inhibits 11 β -hydroxysteroid dehydrogenase type 1 (11 β HSD-1) in adipose/hepatic tissue and may significantly impact the metabolism of cortisol and cortisone. As a consequence, in patients treated with somatropin, previously undiagnosed central (secondary) hypoadrenalism may be unmasked requiring glucocorticoid replacement therapy. In addition, patients treated with glucocorticoid replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses; this may be especially true for patients treated with cortisone acetate and prednisone since conversion of these drugs to their biologically active metabolites is dependent on the activity of the 11 β HSD-1 enzyme.

Excessive glucocorticoid therapy may attenuate the growth promoting effects of somatropin in children. Therefore, glucocorticoid replacement therapy should be carefully adjusted in children with concomitant GH and glucocorticoid deficiency to avoid both hypoadrenalism and an inhibitory effect on growth.

Limited published data indicate that somatropin treatment increases cytochrome P450 (CP450) mediated antipyrine clearance in man. These data suggest that somatropin administration may alter the clearance of compounds known to be metabolized by CP450 liver enzymes (e.g., corticosteroids, sex steroids, anticonvulsants, cyclosporine). Careful monitoring is advisable when somatropin is administered in combination with other drugs known to be metabolized by CP450 liver enzymes. However, formal drug interaction studies have not been conducted.

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral agent may require adjustment when somatropin therapy is initiated (see [PRECAUTIONS, General](#)).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis, mutagenesis and reproduction studies have not been conducted with TEV-TROPIN®.

Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with TEV-TROPIN®. It is not known whether TEV-TROPIN® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. TEV-TROPIN® should be given to a pregnant woman only if clearly needed.

Nursing Mothers

There have been no studies conducted with TEV-TROPIN® in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TEV-TROPIN® is administered to a nursing woman.

Geriatric Use

The safety and effectiveness of TEV-TROPIN® in patients aged 65 and over has not been evaluated in clinical studies. Elderly patients may be more sensitive to the action of somatropin, and therefore may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients.

Adverse Reactions

Utilizing a double-antibody immunoassay, no antibodies to growth hormone could be detected in a group of 164 naïve and previously treated clinical trial patients after treatment with TEV-TROPIN® for up to 40 months. However, utilizing the less specific polyethylene glycol (PEG) precipitation immunoassay, 27 of the 164 patient group were tested after treatment with TEV-TROPIN® for 4 to 6 months and antibodies to growth hormone were detected in two patients (7.4%). The binding capacity of the antibodies from the two antibody positive patients was not determined.

None of the patients with anti-GH antibodies in the clinical studies experienced decreased linear growth response to TEV-TROPIN® or any other associated adverse event. Growth hormone antibody binding capacities below 2 mg/L have not been associated with growth attenuation. In some cases, when binding capacity exceeds 2 mg/L, growth attenuation has been observed.

In studies of growth hormone-deficient children, headaches occurred infrequently. Injection site reactions (e.g., pain, bruise) occurred in 8 of the 164 treated patients.

Leukemia has been reported in a small number of patients treated with other growth hormone products. It is uncertain whether this risk is related to the pathology of growth hormone deficiency itself, growth hormone therapy, or other associated treatments such as radiation therapy for intracranial tumors.

Overdosage

The recommended dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight 3 times per week should not be exceeded. Acute overdose could cause initial hypoglycemia and subsequent hyperglycemia. Repeated use of doses in excess of those recommended could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess human growth hormone.

Dosage and Administration

A dosage of up to 0.1 mg/kg (0.3 IU/kg) of body weight administered 3 times per week by subcutaneous injection is recommended. The dosage schedule for TEV-TROPIN® should be individualized for each patient. Subcutaneous injection of greater than 1 mL of reconstituted solution is not recommended.

After the dose has been determined, each vial of TEV-TROPIN® should be reconstituted with 1 to 5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved).^{*} The stream of normal saline should be aimed against the side of the vial to prevent foaming. Swirl the vial with a GENTLE rotary motion until the contents are completely dissolved and the solution is clear. DO NOT SHAKE. Since TEV-TROPIN® is a protein, shaking or vigorous mixing will cause the solution to be cloudy. If the resulting solution is cloudy or contains particulate matter, the contents MUST NOT be injected.

^{*} Benzyl alcohol as a preservative in bacteriostatic normal saline, USP, has been associated with toxicity in newborns. When administering TEV-TROPIN® to newborns, reconstitute with sterile normal saline for injection, USP.

Occasionally, after refrigeration, some cloudiness may occur. This is not unusual for proteins like TEV-TROPIN® growth hormone. Allow the product to warm to room temperature. If cloudiness persists or particulate matter is noted, the contents MUST NOT be used.

Before and after injection, the septum of the vial should be wiped with rubbing alcohol or an alcoholic antiseptic solution to prevent contamination of the contents by repeated needle insertions. It is recommended that TEV-TROPIN® be administered using sterile disposable syringes and needles. The syringes should be of small enough volume that the prescribed dose can be drawn from the vial with reasonable accuracy.

Stability and Storage

Before Reconstitution – Vials of TEV-TROPIN® are stable when refrigerated at 36° to 46°F (2° to 8°C). Expiration dates are stated on the labels.

After Reconstitution – Vials of TEV-TROPIN® are stable for up to 14 days when reconstituted with bacteriostatic 0.9% sodium chloride (normal saline), USP, and stored in a refrigerator at 36° to 46°F (2° to 8°C). Do not freeze the reconstituted solution.

How Supplied

TEV-TROPIN® (somatropin, rDNA origin, for injection) is supplied as 5 mg (15 IU) of lyophilized, sterile somatropin per vial, in a box containing one vial of TEV-TROPIN® (5 mg per vial) and one vial of diluent [5 mL of bacteriostatic 0.9% sodium chloride for injection, USP (benzyl alcohol preserved)].

Manufactured In Israel By:

BIO-TECHNOLOGY GENERAL (ISRAEL) LTD.

Be'er Tuvia, Israel

Distributed By:

GATE PHARMACEUTICALS

div. of Teva Pharmaceuticals USA

Sellersville, PA 18960

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